# NON-CONTRASTED COMPUTED TOMOGRAPHY FOR THE ACCURATE MEASUREMENT OF LIVER STEATOSIS IN NON ALCOHOLIC FATTY LIVER DISEASE

**Dissertation submitted for**

**D.M.DEGREE EXAMINATION- AUGUST-2013**

**BRANCH-IV-MEDICAL GASTROENTEROLOGY**

**MADRAS MEDICAL COLLEGE**

**&**

**RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL**

**CHENNAI-600003**

**THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY**

**CHENNAI-600032**

# CERTIFICATE

This is to certify that the dissertation **"NON-CONTRASTED COMPUTED TOMOGRAPHY FOR THE ACCURATE MEASUREMENT OF LIVER STEATOSIS IN NON ALCOHOLIC FATTY LIVER DISEASE"** is a bonafide work of **Dr.P.SENTHIL KUMAR** in partial fulfillment of the requirements for D.M. Branch-IV (MEDICAL GASTROENTEROLOGY) examination of THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY to be held in August 2013.The period of post-graduate study and training was from August 2010 to July 2013.

**DR. MOHAMMED ALI., MD., DM.,**
PROFESSOR AND HOD
MADRAS MEDICAL COLLEGE,
CHENNAI

**DEAN**
MADRAS MEDICAL COLLEGE,
CHENNAI

# DECLARATION

**I, Dr. P.SENTHIL KUMAR,** solemnly declare that this dissertation entitled, **NON-CONTRASTED COMPUTED TOMOGRAPHY FOR THE ACCURATE MEASUREMENT OF LIVER STEATOSIS IN NON ALCOHOLIC FATTY LIVER DISEASE** is a bonafide work done by me at the Department of Medical Gastroenterology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai during the period 2010- 2013 under the guidance and supervision of the Prof. Mohammed Ali M.D.,D.M., Professor and Head of the Department Of Medical Gastroenterology of Madras Medical College & Government General Hospital, Chennai.

This dissertation is submitted to The Tamil Nadu Dr.M.G.R Medical University, towards requirement for the award of D.M. Degree (Branch-IV) in Medical Gastroenterology

Chennai
Date

**Dr. P.SENTHIL KUMAR**
Post graduate student
D.M(Medical Gastroenterology)
Madras Medical college, Chennai-3.

# ACKNOWLEDGEMENTS

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In addition, I am grateful to of my copost graduate students for helping me out throughout this study period.Last but not the least I thank all my patients for their kind cooperation

# CONTENTS

# ABBRIVATIONS

| | | |
|---|---|---|
| ncCT | - | Non-Contrasted Computed Tomography |
| LFT | - | Liver Function Test |
| CTHU | - | Computer Tomography in Houns Field Unit. |
| CTL-S | - | Computer Tomography of Liver – spleen in Houns Field Unit. |
| CTL/S | - | Computer Tomography of Liver to spleen ratio in Houns Field Unit. |
| BMI | - | Body Mass Index |
| NASH | - | Non Alcoholic Steato Hepatitis |
| NAFLD | - | Non Alcoholic Fatty Liver Disease |

# INTRODUCTION

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Non alcoholic fatty liver disease[NAFLD] is emerging as most common liver disorder in India and other developing countries, The histological spectrum ranging from simple steatosis or steatosis with only mild inflammation (type 1 and 2 NAFLD) to more severe steatohepatitis (types 3 and 4 NAFLD or NASH). Types 3 and 4 NAFLD progress to cirrhosis in 15-20% of patients. Progression is silent or paradoxically associated with normalization of aminotransferases. **"**NASH" coined by Ludwig and colleagues from Mayo clinic.

**SPECTRUM OF NAFLD**

- Steatosis
- Steatohepatitis (NASH)
- NASH with Fibrosis
- Cirrhosis

**DEFINITIONS**

**NAFLD**: Non alcoholic fatty infiltration with no or minimal inflammation and no fibrosis.also called simple steatosis,Pure steatosis and bland steatosis.

**Primary NAFLD** : indicates typical NAFLD associated with central obesity and T2 DM without specific etiology.

**Secondary NAFLD** – associated with a specific, non alcohol related problem such as drugs or toxins.

**Toxin- associated steatohepatitis** : associated with specific toxin or medication.eg petrochemical exposure in oil industry

## CRITERIA FOR DEFINING NAFLD

1) A liver biopsy showing moderate to gross macrovesicular fatty change with or without inflammation (lobular or portal),and Mallory bodies, fibrosis, or cirrhosis.
2) No alcohol consumption or consumption less than 40 g of ethanol per week.
3) Absence of serologic evidence of hepatitis B or hepatitis C.

## EPIDEMIOLOGY AND PREVALENCE

Prevalence of NAFLD 13-18% and that of NASH specifically 2-3% (1.2-9%) in two Japanese studies- incidence rate of 31 and 86 cases . ( AGA guidelines 2012)

The prevalence of NAFLD defined by USG -46%

By histology confirmed NASH-12.2 %. (AGA guidelines 2012) It is a disease of all sexes, ethnicities, and age groups (peak 40-59) Higher in Hispanics than Africa Americans. Occurs more frequently in females (65 to 83%)

**OBESITY**

4.6 fold increase risk of fatty liver in USG compared to nonobese. Autopsy studies, steatosis-approx 70%obese vs 35% lean. Severe obesity patients- prevalance of NAFLD may go upto 90%. Obese patients with abnormal liver enzymes approx 30% has septal fibrosis and 10% cirrhosis.

**INSULIN RESISTANCE AND T2 DM**

Insulin resistance is very common in NAFLD. Progression to overt iabetes is preceded by steatosis in susceptible population. 75% of T2 DM-fatty infiltration. Liver injury worsens the preexistant diabetes in patients with NAFLD and doubles the prevalence of cirrhosis from 10-25%.

**HYPERLIPIDEMIA**

2/3 of hypertriglyceridemeia&1/3$^{rd}$ with hypercholestrolemia- fatty liver Hyperlipidemia reported in 92% of NASH patients. Ethnic variation in lipid metabolism. Heterogenicity in lipid phenotypes in NAFLD

## METABOLIC SYNDROME

Steatosis and central adiposity with underlying insulin resistance and lipotoxicity- independent risk factor for metabolic syndrome. Unexplained elevation of liver enzymes attributable to NAFLD seen in 7% of individuals with metabolic syndrome defined by adult Treatment Panel 111 criteria.

## DIAGNOSIS

On routine liver biochemical test elevated liver enzymes level usually will suspect common causes of liver disease will arose for other investigations like USG, CT, MRI, CBC, PT, anti-HCV, HBsAg, serum iron , anti-tripsin, ANA, on physical examination hepatomegaly, on history alcohol consumption should be excluded [ less than 40 grams /week] clinically if the patients having age > 50 years, obesity, diabetes, hypertension

## IMAGING

Hepatic ultrasonogram shows “bright liver” with increased echoes consistant with steatosis on CT scan. Fatty liver shows lower in density compared to screen, MRI shows fat appears bright on T1 – weighted image, combination USG and CT have sensitivity 93 – 100% for detecting

hepatic fat, with more than grade I fatty liver [< 5% is minimal, 5 – 33% grade I, 33 – 66% grade II, > 66% grade III] with positive predictive value of 62 – 76%, no radiologic modality able to distinguish simple steatosis from more advanced NAFLD. These imaging techniques [USG, CT, MRI, support the diagnosis of NAFLD but it cannot predict the severity of disease. And also it cannot replace gold standard liver biopsy and histopathogy, for establishing diagnosis in certainty.

So The degree of steatosis in NAFLD patients is usually assessed with invasive technique like liver biopsy, because of the invasive method of the liver biopsy and its painful nature of the procedure with moderate complication rate need to find alternative less invasive, less painful, quick method to accurately diagnose NAFLD

# AIM OF THE STUDY

# AIMS AND OBJECTIVES

To study and analyse unenhanced CT [nc-CT] determination of hepatic steatosis based on image attenuation data (Hounsfield units) and to correlate it with liver histopathology

# REVIEW OF LITERATURE

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NAFLD is emerging as one of the most common liver disorder in India and many other developing countries in the world. The histological spectrum ranging from simple steatosis or steatosis with only mild inflammation( type 1 and 2 NAFLD) to more severe steatohepatitis (types 3 and 4 NAFLD or NASH. Types 3 and 4 NAFLD progress to cirrhosis in 15-20% of patients. Progression is silent or paradoxically associated with normalization of aminotransferases. "NASH" coined by Ludwig and colleagues from Mayo clinic.

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The prevalence by USG is-46% and the prevalence by histology -12.2 %. (AGA guidelines 2012)

It is a disease of both the sexes, ethnicities, and all age groups (peak 40-59) higher in Hispanics than Africa Americans. Occurs more frequently in females (65 to 83%)

**OBESITY**

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## METABOLIC SYNDROME

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## GENETIC AND FAMILIAL FACTORS

Ethnic variation: Hispanic descent in USA has higher prevalence of NASH than primarily african-american descent. It reflects the ethnic difference in body fat distribution and lipoprotein metabolism. Familial factors: High prevalence in 1$^{st}$ degree relatives in NASH. Insulin resistance among relatives of T2DM and impaired skeletal muscle mitochondrial metabolism in offspring supports genetic component. Genetic variation: gene coding phospholipase like protein called PNPLA3 or adiponutrin – major predictor of steatosis in different ethnic groups.

## NASH in other liver diseases

Steatosis mediated by core protein metabolism and microsomal TGL transfer protein associated with hepatitis C {geno3} infection. Obesity, insulin resistance negatively influences response to antiviral therapy. Occult hemochromatosis and iron loading – cofactor in progression of NASH. Steatosis –potential factor in progression of PBC.

## ETIOLOGY

### Causes of Nonalcoholic Fatty Liver Disease

### Acquired Metabolic Disorders

- Diabetes mellitus
- Dyslipidemia
- Kwashiorkor and marasmus
- Obesity
- Starvation

### Cytotoxic and Cytostatic Drugs

### Other Drugs and Toxins

- Amiodarone
- 4,4′-diethylaminoethoxyhexestrol
- Dichlorethylene
- Ethionine
- Ethyl bromide
- Estrogens
- Glucocorticoids
- Highly active antiretroviral therapy
- Hydrazine
- Hypoglycin

- Orotate
- Perhexilene maleate
- Safrole
- Tamoxifen

**Acquired Metabolic Disorders**

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- Hydrazine
- Hypoglycin
- Orotate
- Perhexilene maleate
- Safrole
- Tamoxifen

**Metals**

- Rare earths of low atomic number
- Thallium compounds
- Uranium compounds

**Inborn Errors of Metabolism**

- Abetalipoproteinemia
- Familial hepatosteatosis
- Galactosemia
- Glycogen storage disease
- Homocystinuria

- Systemic carnitine deficiency
- Tyrosinemia
- Weber-Christian syndrome
- Wilson disease

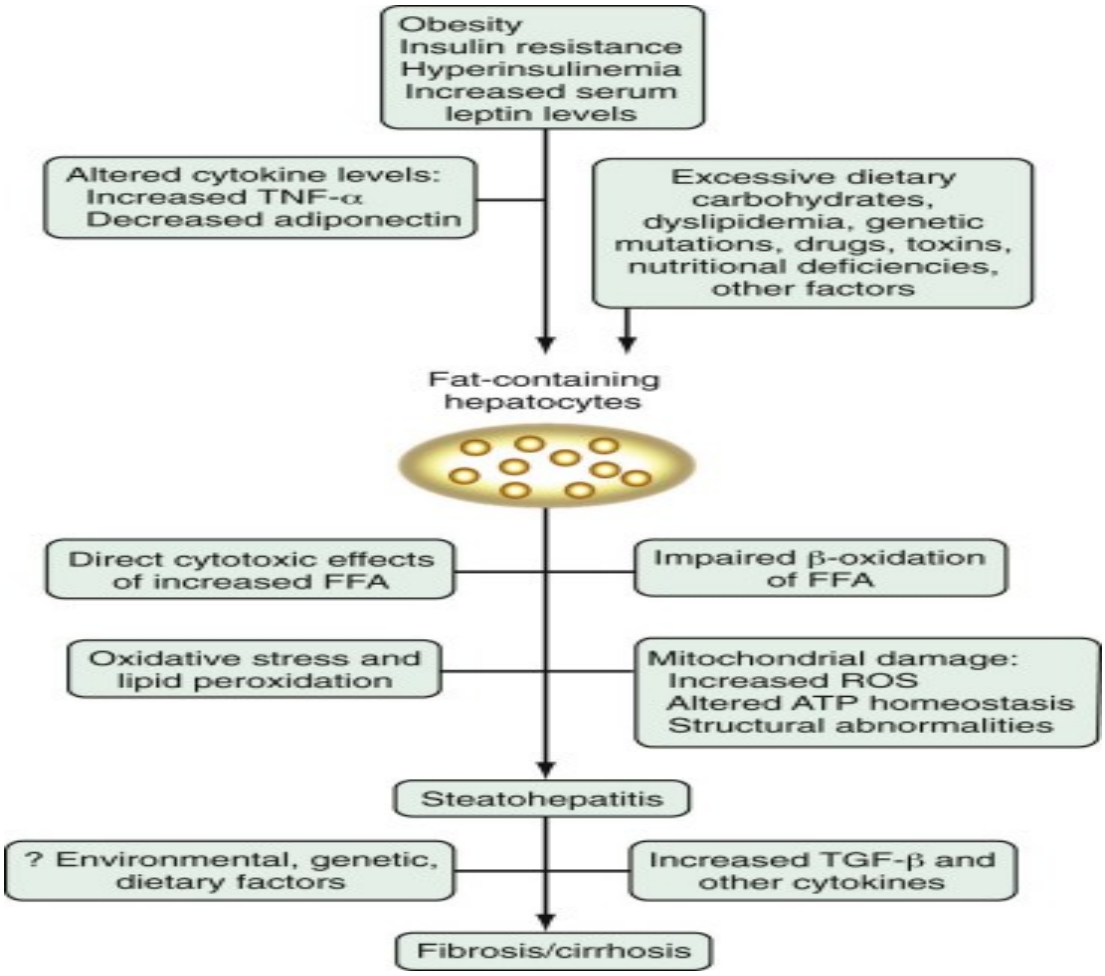
**Surgical Procedures**

- Biliopancreatic diversion
- Extensive small bowel resection
- Gastric  and
- Jejunoileal bypass

**Miscellaneous Conditions**

- Industrial exposure to petrochemicals
- Inflammatory bowel disease
- Partial lipodystrophy
- Jejunal diverticulosis with bacterial overgrowth
- Severe anemia
- Total parenteral nutrition

## PATHOGENESIS OF NAFLD




## TRIGLYCERIDE ACCUMULATION

Occurs due to shifting of fatty acid metabolism to lipogenesis and also synthesis of lipoprotein decreases

- Excessive importation of FFA

Obesity

- Impaired VLDL synthesis and secretion
- Impaired beta-oxidation of FFA to ATP

**INSULIN RESISTANCE& HYPERINSULINEMIA**

It is a Primary pathogenic factor in steatosis. Excess FFA causes insulin resistance by down regulating IRS-1 signaling. Insulin resistance potentiated by aberrant function of peptide mediators TNF-α,leptin and adiponectin. TNF-α downregulates IRS-1 signaling via serine phosphorylation through activation of Jun terminal N kinase . Activation of inhibitor Kappa βkinase / nuclear factor kappa β by FFA – reduce insulin sensitivity.

**LIPID PEROXIDATION & HEPATIC LIPOTOXICITY**

FFA upregulates cyst P-450 – enhanced generation of ROS & lipid per oxidation. Increase FFA concentration –sustained upregulation of PPAR-α-promotes fatty acid oxidation. FFA – direct toxicity to cell membrane- toxic fatty acid ethylesters formation – disruption of mitochondial function. Adiponectin and Leptin

**Other mechanisms**

- Portal endotoxemia
- Oxidative stress- induction of cyt P450 2E1- generate ROS – peroxidase cellular membrane- cell injury.
- Mitochondrial changes

  - Mitochondrial ROS formation

  - Megamitochondria and crystalline inclusions

  -Structural abnormalities

  -Altered ATP homeostasis

**Clinical features**

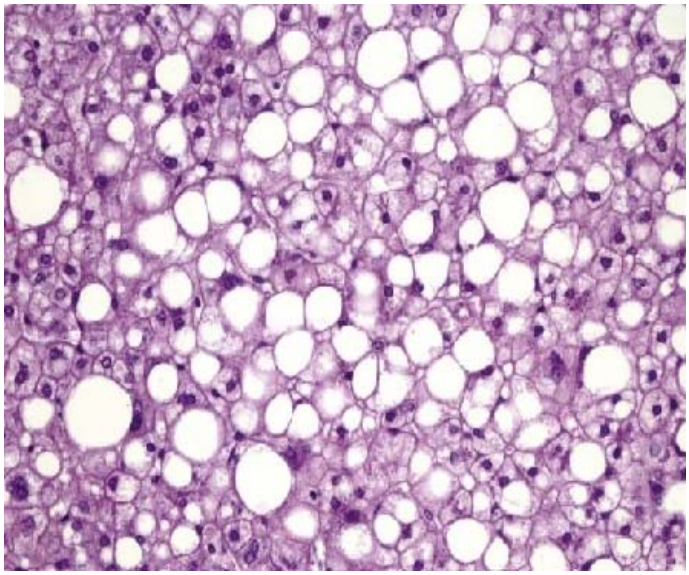
**Clinical and Laboratory Features of Nonalcoholic Fatty Liver Disease**

| SYMPTOMS | SIGNS | LAB FEATURES |
|---|---|---|
| **Common** | | |
| None (48-100%)<br>Fatigue (70%) | Hepatomegaly | 2 to 4 fold elevation of ALT/AST levels |
| RUQ pain (50%) | | AST/ALT ratio <1 |
| | Acantosis nigricans | S.ALP slightly elevated |
| | Occasional Neurological Deficits. In children | Normal biluribin and albumin&PT levels<br>Elevated serum ferritin levels.<br>Increase in uric acid levels |
| **Uncommon** | | |
| Vague right upper quadrant pain | Splenomegaly | Low titre<1:320)ANA positivity |
| Fatigue | Spider angiomata | Elevated transferrin saturation |
| Malaise | Palmar erythema | HFE gene mutation ( C282Y) |
| | Ascites | Elevation serum Ig A |

## NAFLD and Normal Aminotranferases

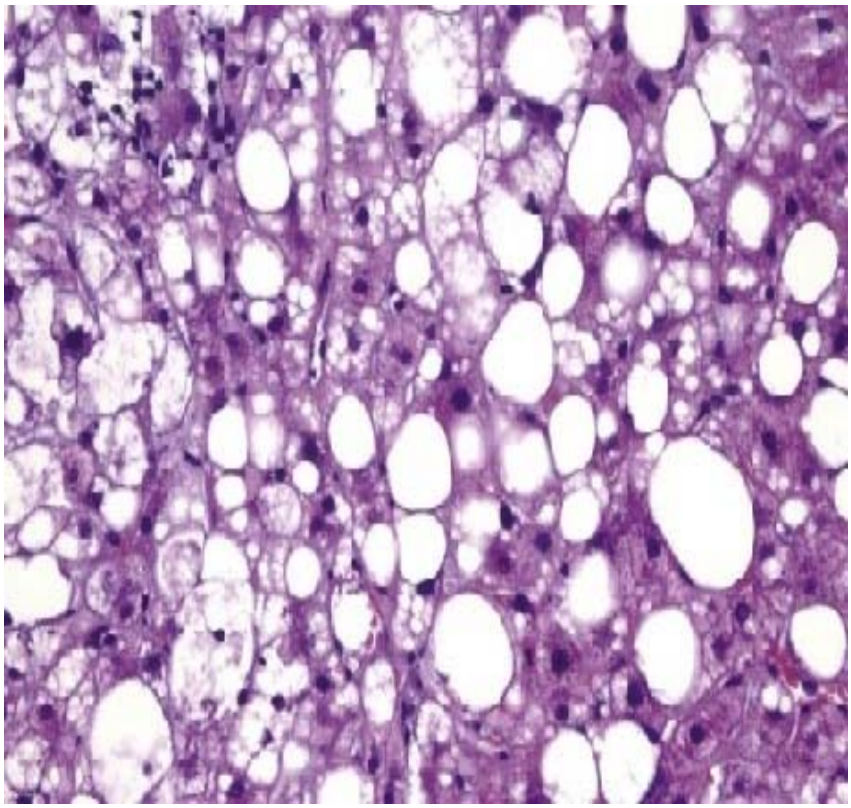
- Occurs in later stages of steato hepatitis.
- “True normal” in obese patients may be lower than that of lean individuals.
- ALT levels are positively correlated with central obesity and hyperinsulinemia(leading to ongoing effort to revise normal changes).
- Glitazones normalise transminase levels,but stil criteria for NASH met on follow up liver biopsy.

### Histopathology of NAFLD



- Picture of simple steatosis or fatty liver.
- Glycogenated nuclei seen.

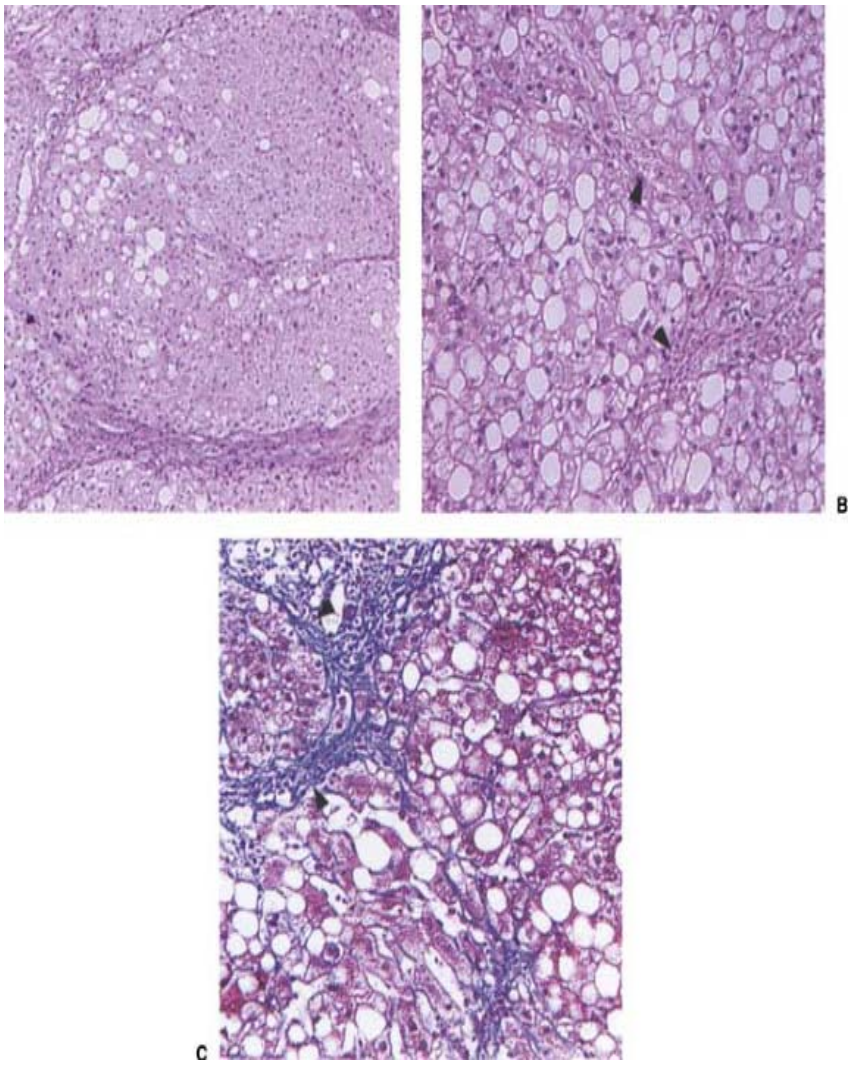
**NASH**



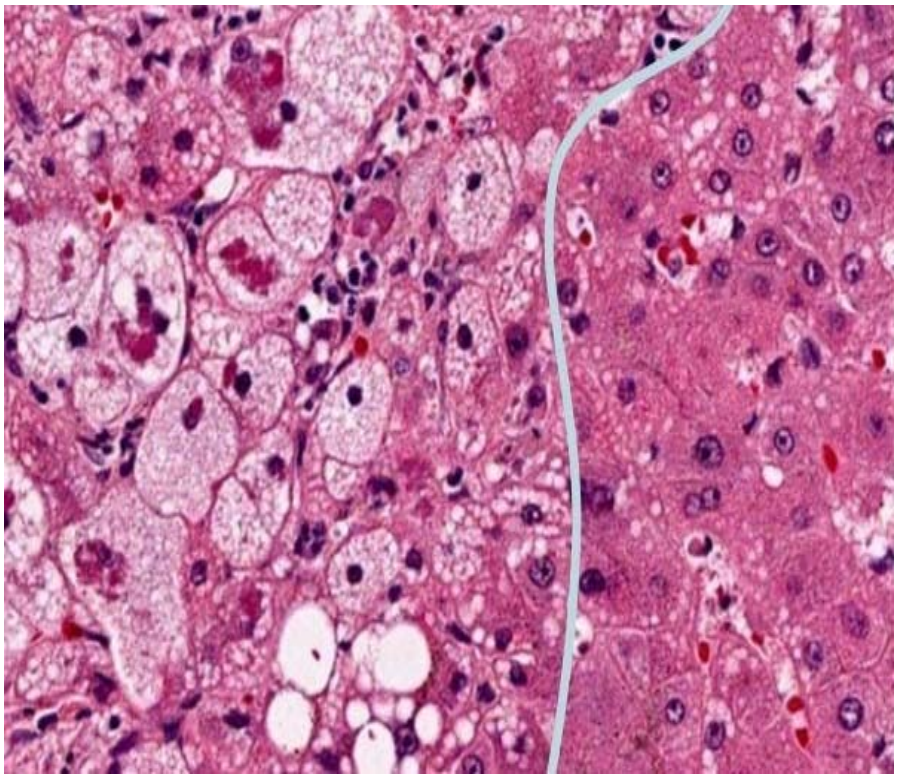
- “Lobular inflammation” is hallmark.

- Hepatocyte ballooning and necrosis of varying degrees present.

**NASH with cirrhosis**




- NASH with cirrhosis ( macrovesicular steatosis,inflammation and cirrhosis)
- Early Cirrhosis (bridging fibrosis)
- Masson trichrome staining.



- Mallory – Denken bodies – perinuclear material- dark staining brown masses.

**Histological Features of NAFLD**

Present in All or Most Cases

- Macrovesicular steatosis
- Diffuse or centrilobular steatosis; degree may correlate with BMI
- Parenchymal inflammation
- Polymorphonuclear neutrophils, lymphocytes, other mononuclear cells
- Hepatocyte necrosis
- Ballooning hepatocyte degeneration

**Observed with Varied Frequencies**

- Perivenular, perisinusoidal, or periportal fibrosis (37%-84%), moderate to severe in 15%-50%; most prevalent in zone 3 (perivenular)
- Cirrhosis (7%-16% on index biopsy specimen)
- Mallory bodies
- Glycogenated nuclei
- Lipogranulomas
- Stainable hepatic iron

**Risk Factors for Advanced Nonalcoholic Fatty Liver Disease**

**Clinical**

- Older age (>50 years)
- Obesity
- Diabetes mellitus/insulin resistance
- Hypertension

**Laboratory**

- AST/ALT ratio > 1
- Serum ALT level > twice the upper limit of normal
- Serum triglyceride levels > 155 mg/Dl

**Histologic**

- Severe steatosis
- Necroinflammatory activity (hepatocyte ballooning, necrosis)
- Stainable iron

**Diagnostic approach and evaluation of NAFLD.**

**Essential Recording**

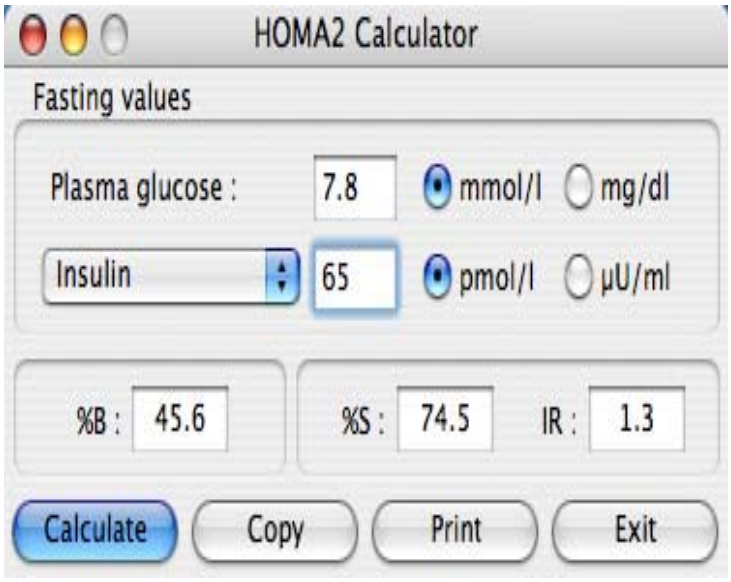
- Age, Gender
- Body weight, body height, waist circumference, hip circumference, BMI
- Alcohol consumption (amount/frequency, at least g/day)

- History of liver disease, including HBV, HCV, autoimmune disease, DM, hyperlipidimia
- Family History of above mentioned (at least first degree)

**NAFLD and Related Biochemical Studies Including OGTT and, IR**

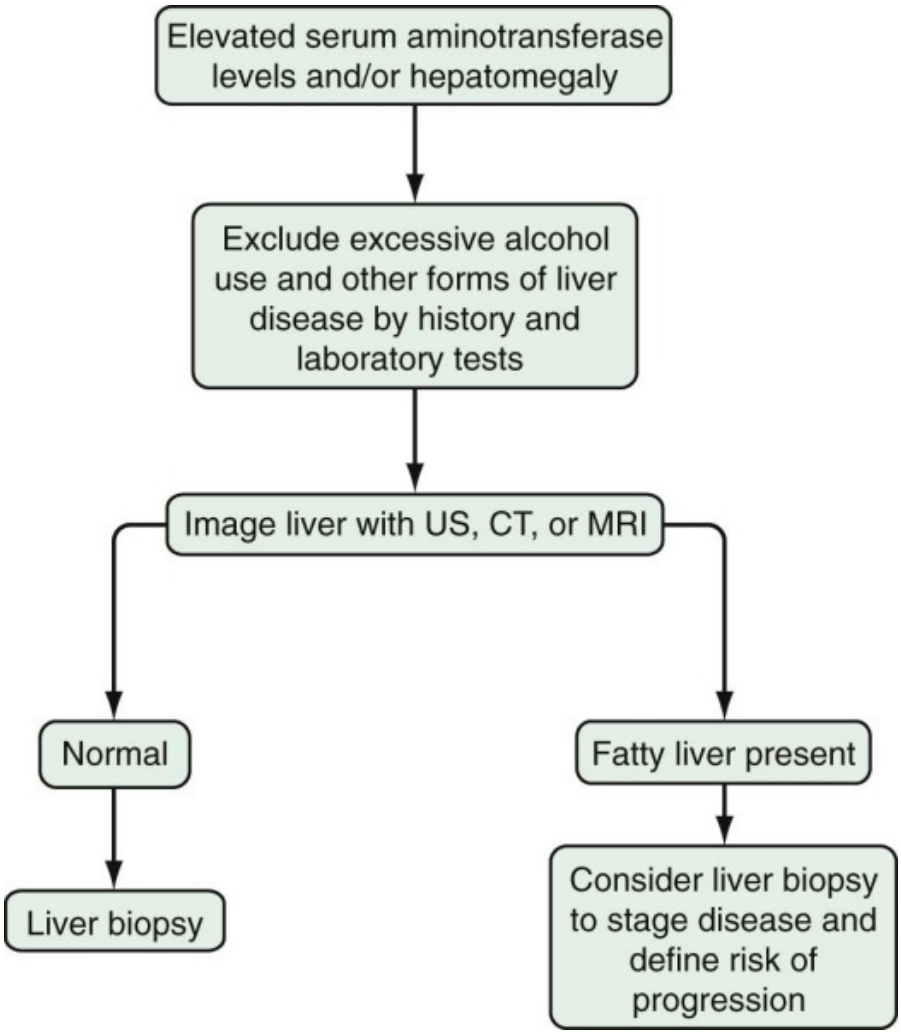
- Arthrometry: BMI, Wait/hip ratio
- AST/ALT, rGT, Bilirubin, ALP
- Cholesterol, HDL, TG, UA
- SBP/DBP
- OGTT
- Insulin Resistance
- ANA, Ferritin

## HOMA &QUICKI




- Used to estimate insulin resistance by utilising mathematical manipulation of fasting insulin and glucose levels.
- Homa index: insulin concentration (µU/ml)x fasting glucose concentration (mmol/l)/22.5 - utilise
- Cutoff level: 2.5 for adult
- Cutoff level: 3.16 for aldolescent
    - Keskin M, et al. Padiactric 2005 March
    - QUICKI ( quantitative insulin sensitivity index)- the addition of free fatty acid level in this will improve the accuracy

**Diagnostic approach in suspected NAFLD**



**Role of Liver biopsy**

The only diagnostic test that quantifies hepatic steatosis,necrosis and fibrosis and histological stage of NAFLD is best prognostic indicator.

- Indications in

  NAFLD:

  Peripheral stigmata of chronic liver disease

  Splenomegaly

  Cytopenia

  Abnormal iron studies

  Diabetes and/or significant obesity in an individual over the age of 45

**BIOPSY SCORING**

- NASH grade and stage(brunt) 0-8
- NASH activity index ( NAI)- 0-12 accounts for steatosis, necroinflammatory and hepatocyte injury

  NAFLD activity score ( NAS)-0-8,steatosis 0-3,lobular and portal inflammation 0-3 cellular ballooning 0-2

**NAFLD—Natural History**

- Steatosis generally follows a benign course
- Steatosis can progress to NASH ± fibrosis
- NASH with fibrosis has increased liver-related morbidity and mortality
- Olmsted large study 420pts with definite NAFLD on imaging and biopsy findings

  cirrhosis developed in 3% of patients.

- 132 patients of NAFLD followed for 18yrs.

  clinical outcomes based on degree of injury on an index liver biopsy specimen.

  Cirrhosis and liver related death are common in NAFLD types 3 and 4 than 1 and 2.

- Studies show that long term survival of patients with NASH significantly better than alcoholic hepatitis .
- 5-10yr outcome of NAFLD associated cirrhosis was similar to that for HCV associated cirrhosis, although HCC less common in patients with NAFLD.

- Studies show that long term survival of patients with NASH significantly better than alcoholic hepatitis .

**Independent predictors of fibrosis progression**

- Diabetes mellitus,
- Low initial fibrosis stage
- Higher body mass index.
- Elevated liver enzymes

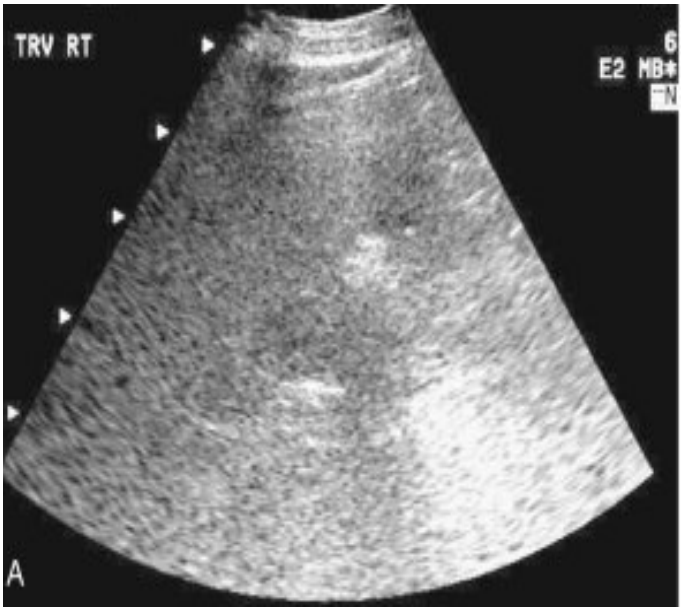
**Non invasive markers of fibrosis in NAFLD**

- Fibrotest: This tests incorporates haptoglobin,bil,GGTP,apo lipoproteinemiaA-1, α2 macroglobulin and necroinflammatory index combines above markers plus ALT levels. cut off value – 0.70 has pos predictive value
- NAFLD fibrosis score : incorporates age ,BMI,hyperglycemia, AST/ALT ratio, platelet count and serum albumin level. PPV of 82-90%
- Transient elastography (fibro scan)
- S.dehydroepiandrosterone
- S.hylaluronic acid levels.
- Recently cytokeratin -18 level – novel biomarker for NASH

**IMAGING OF NAFLD**

- USG abdomen - "bright " liver of increased echogenicity.

Poor detection if the degree of steatosis is less than 20% to 30% Initial test of choice for large population screening.




- **CT imaging :**

Sensitivity and specificity of detecting fatty liver (with spleen-minus-liver attenuation of 10 Hounsfield units) were 0.84 and 0.99. liver: spleen ratio <1- steatosis

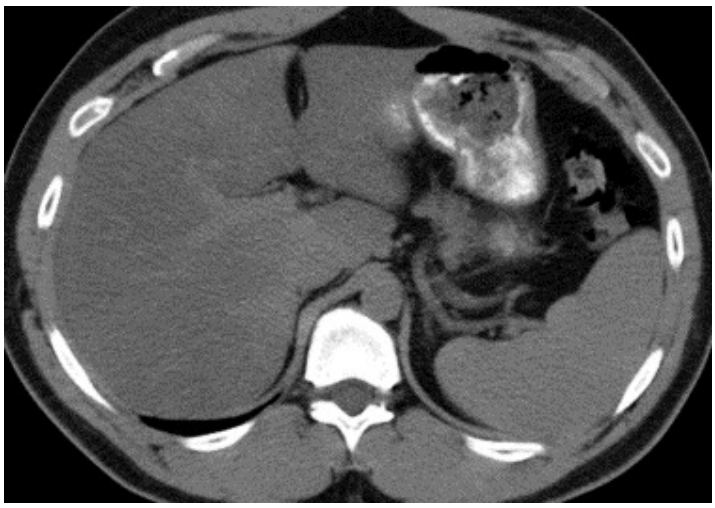
- **MRI :**

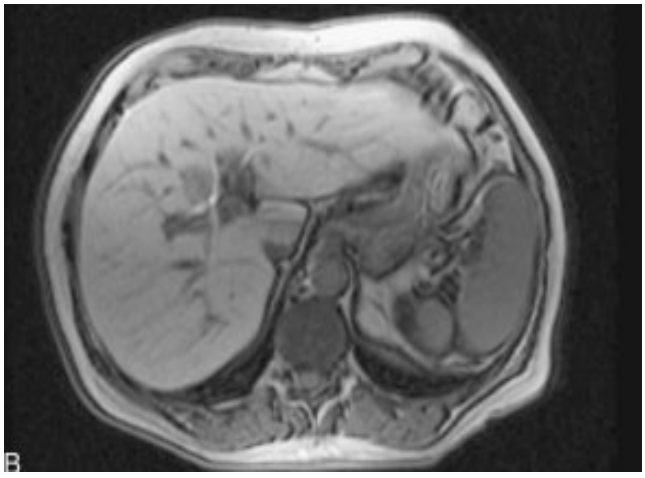
T 1weighted image shows bright liver.

Dixon technique provides qualitative assessment of TGL content.

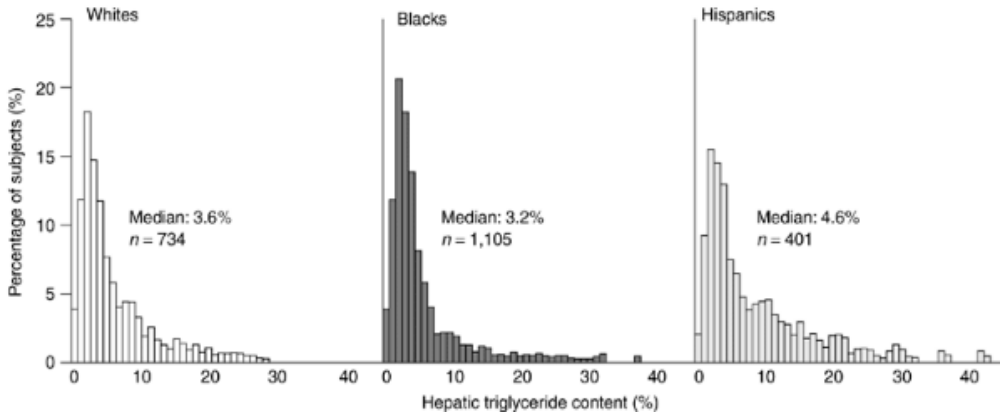
- **MR proton spectroscopy :**

Newer tecnique of quantification of fatty infiltration.most accurate method of quantifying steatosis





**MR spectroscopy of TGL content in different ethnics**




Currently non-invasive modalities are unable to detect NASH with or without fibrosis

# MATERIALS AND METHODS

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The study was conducted at the department of Medical Gastroenterology, Institute of Pathology and in the Bernard Institute of Radiology Department in the Rajiv Gandhi Government General Hospital Chennai. and in the Madras Medical College Chennai.,

Patients coming to our OPD undergo routine investigations like CBC,LFT,RFT,Blood sugar and USG Abdomen, among them those who had fatty liver on USG abdomen were selected, those who with history of alcohol use and viral hepatitis were excluded

| | |
|---|---|
| **Inclusion criteria** | 1. Fatty liver on USG Abdomen |
| **Exclusion criteria** | 1. Alcohol (more than 20 g/d)<br>2. HCV infection<br>3. HBV infection<br>4. Decompensated CLD<br>5. HCC / focal lesion on USG or CT<br>6. Coagulopathy ( for liver Bx)<br>7. Secondary cause- surgery, Drugs, Pregnancy |

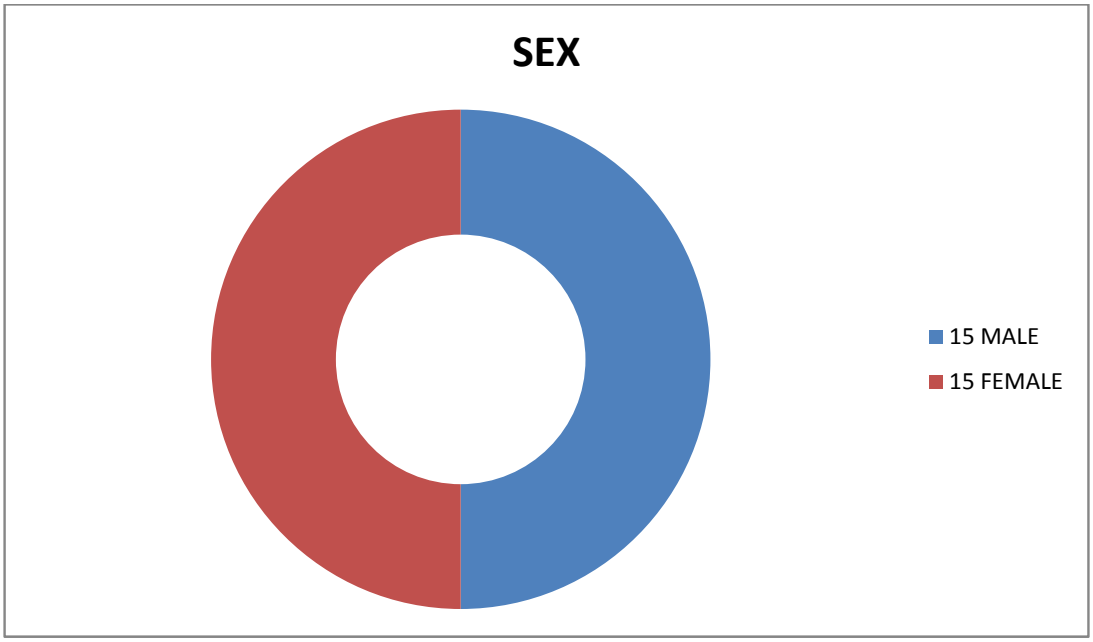
Total no of patients selected from the study is 30

**Table 1**

**SEX DISTRIBUTION**

| SEX DISTRIBUTION | CASES |
|---|---|
| MALE | 15 |
| FEMALE | 15 |

**SEX DISTRIBUTION**

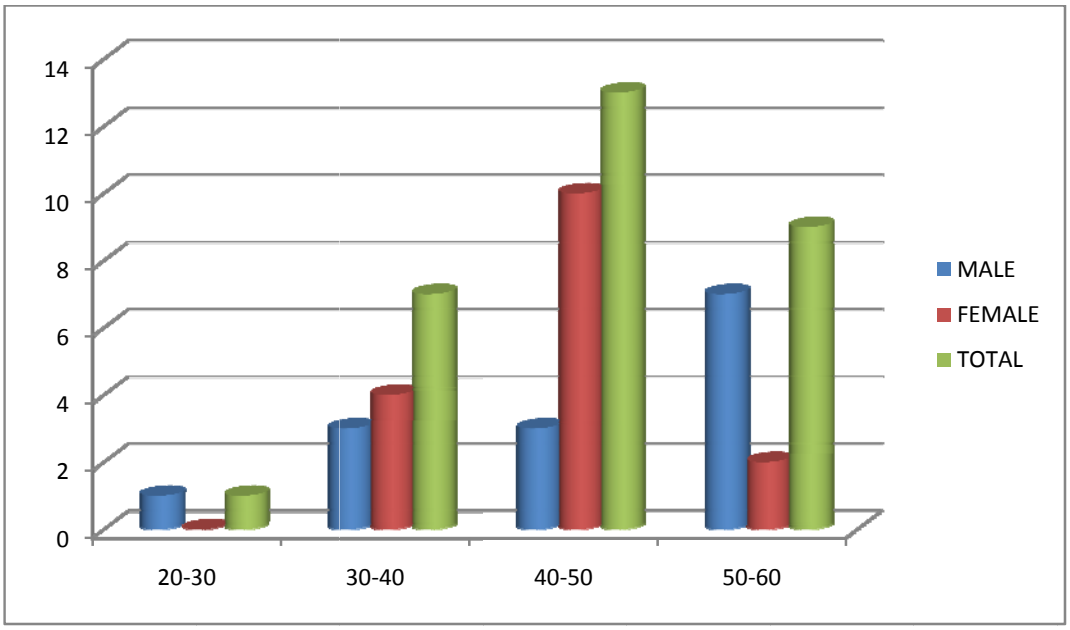


## Table 2

## AGE DISTRIBUTION

| AGE DISTRIBUTION | MALE | FEMALE | TOTAL |
|---|---|---|---|
| 20-30 | 1 | 0 | 1 |
| 30-40 | 4 | 3 | 7 |
| 40-50 | 3 | 10 | 13 |
| 50-60 | 7 | 2 | 9 |

## AGE DISTRIBUTION

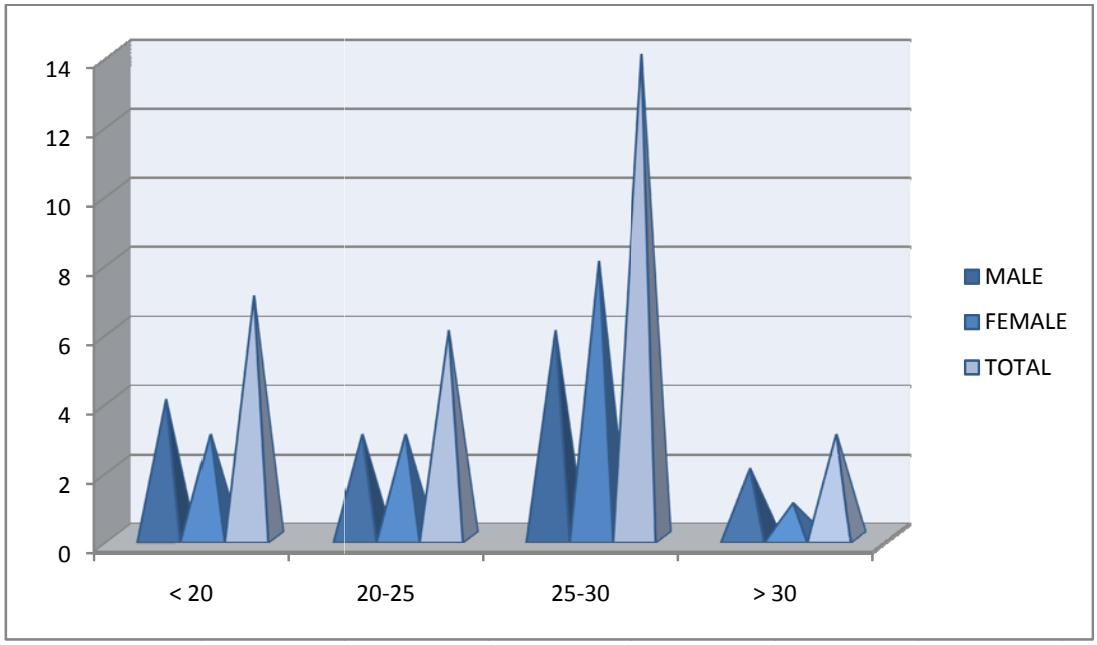


## Table 3

## BMI CHART

| BMI | MALE | FEMALE | TOTAL |
|---|---|---|---|
| < 20 | 4 | 3 | 7 |
| 20-25 | 3 | 3 | 6 |
| 25-30 | 6 | 8 | 14 |
| 30-35 | 2 | 1 | 3 |

## BMI CHART



These selected patient subjected to the following additional investigations Biochemical investigation – LFT. HBsAg, anti HCV, BT, CT, PT/INR.

Detailed history was taken and physical examinations done. All the patients underwent non contrast CT [ncCT] scan. those patients underwent non contrast computerized tomography of the abdomen with machine [GE Medical Systems, Milwaukee, WI] of Bernard Institute Of Radiology in Rajiv Gandhi Government General Hospital – Chennai .

Following observation are assessed from the Radiology Department. With Non contrast computerized tomography [nc CT] CT attenuation index in houns field units [HU] of liver and CT attenuation index in houns field units [HU] of spleen were assessed.

All the patients after informed concern underwent liver biopsy after proper aseptic precaution and after screening for coagulation profile in the side room of ward no : 243 and 245 [male and female ward] of Medical Gastro Enterology Department Liver biopsy was done with biopsy true cut biopsy needle using biopsy gun, the specimen was placed in 10% formalin and submitted for histologic examination.

**LIVER BIOPSY GUN**

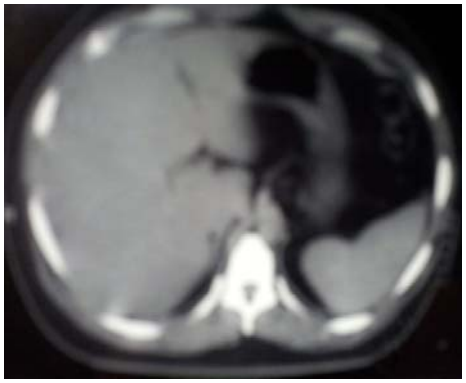
After the liver biopsy all the patients were admitted and observed in the ward for 24 hrs. Successful biopsy specimens were obtained in all the patients among them two patients [mrs.Ayisha bevi and mr.Prasanth] required two pass for adequate biopsy sample size, other 28 patients required one pass only.

Among them one patient [mrs.uniammal] developed severe pain after the procedure [pain radiating to right shoulder and became dyspneic ] she has been screened with X ray chest, X ray erect abdomen and USG Abdomen .no evidence of any pneomothorax noted and the patient was managed symptomatically . no intervention required and sent home after 48 hrs of observation.

# RESULTS

# RESULTS

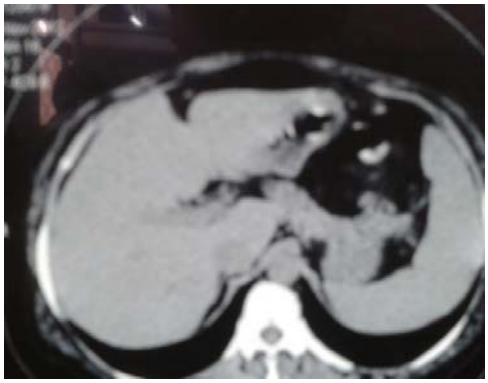
This study includes total of 30 cases- CT Finding of six patients



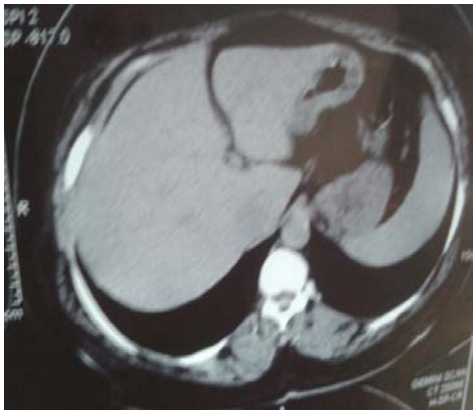
**Mrs.Muniammal**

**Mrs.Nisha**

**Mr.Prasanth**



**Mrs. Priya**



**Mr.Parthiban**

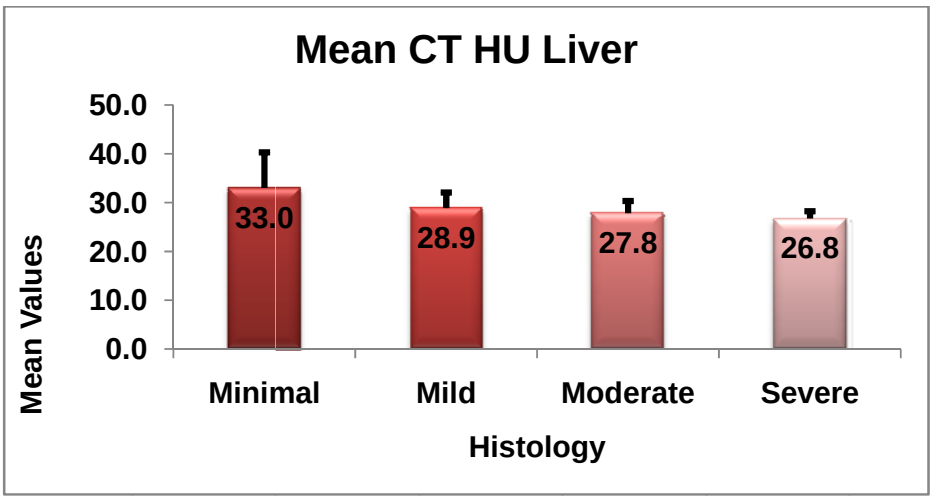
**Mr.Vetri selvan**

**Table 4**

**CT Scan Finding of 30 patients –Attenuation in HOUNS FIELD UNITS [HU]**

| NAME | AGE | SEX | CT HU Liver | CT HU spleen | CT HU Liver-spleen |
|---|---|---|---|---|---|
| Raja | 29 | M | 26 | 49 | -23 |
| Banumathi | 32 | F | 31 | 52 | -21 |
| Devaki | 60 | F | 26 | 45 | -19 |
| Rangasamy | 55 | M | 28 | 47 | -19 |
| Yoganand | 57 | M | 45 | 54 | -9 |
| Aisha bee | 47 | F | 34 | 42 | -8 |
| Purushothaman | 39 | M | 36 | 48 | -12 |
| Ladly | 32 | M | 26 | 48 | -22 |
| Ram mohan | 53 | M | 26 | 49 | -23 |
| Prabha | 44 | F | 26 | 48 | -22 |
| Ramasamy | 55 | M | 26 | 42 | -6 |
| Ayisha bevi | 47 | F | 28 | 45 | -17 |
| Prasanth | 44 | M | 29 | 54 | -25 |
| Jananki | 39 | F | 26 | 42 | -18 |
| Gopi | 43 | M | 28 | 48 | -20 |
| Nisha | 47 | F | 26 | 57 | -25 |
| Priya | 34 | F | 34 | 51 | -17 |
| Jothi | 42 | F | 28 | 45 | -17 |
| Amudha | 48 | F | 28 | 45 | -16 |
| Lalitha | 51 | F | 28 | 45 | -17 |
| Kumar | 45 | M | 31 | 45 | -14 |
| Muniammal | 48 | M | 26 | 45 | -19 |

| | | | | | |
|---|---|---|---|---|---|
| Yogas | 57 | M | 32 | 45 | -13 |
| Vetriselvan | 35 | M | 26 | 56 | -24 |
| Vijayalakshmi | 39 | F | 29 | 45 | -16 |
| Sangeetha | 40 | F | 29 | 48 | -19 |
| Noorjagans | 42 | F | 26 | 48 | -19 |
| Anandvalli | 45 | F | 28 | 45 | -17 |
| Thiru | 51 | M | 26 | 48 | -22 |
| Parthiban | 54 | M | 28 | 50 | -22 |




Among them their biopsy has been graded and its results

**Table 5 (a)**

**BIOPSY GRADING ADOPTED**

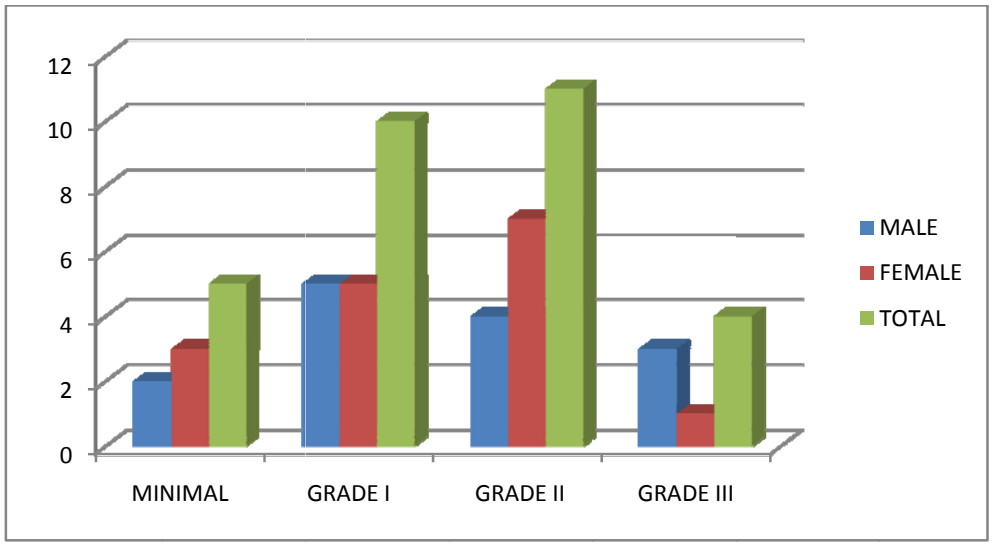
| | |
|---|---|
| Grade 0 | Minimal <5 % steatosis |
| Grade I | 5-33% steatosis |
| Grade II | 33-66 % steastosis |
| Grade III | >66 % steatosis |

**Table 5 (b)**

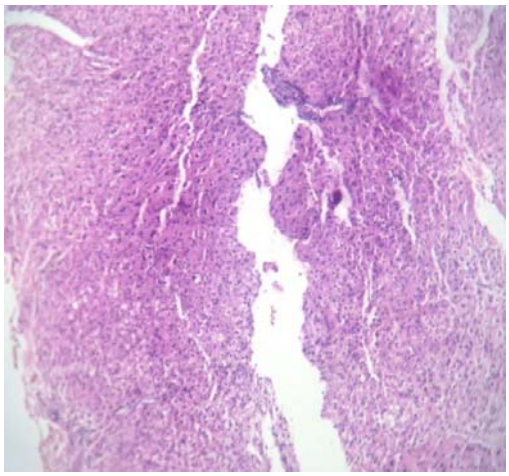
**HISTOLOGICAL GRADE-OBSERVATIONS**

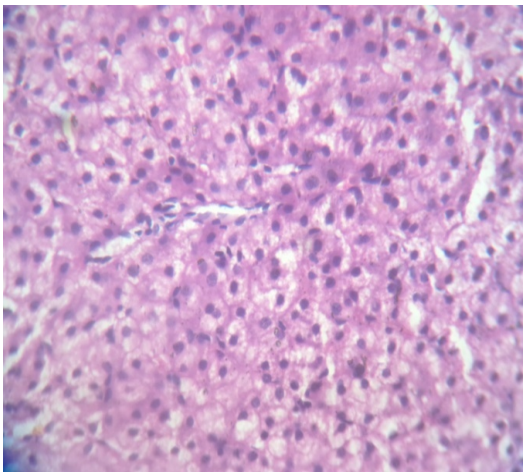
| HISTOLOGIC GRADE | MALE | FEMALE | TOTAL |
|---|---|---|---|
| MINIMAL | 2 | 3 | 5 |
| GRADE I | 5 | 5 | 10 |
| GRADE II | 4 | 7 | 11 |
| GRADE III | 3 | 1 | 4 |

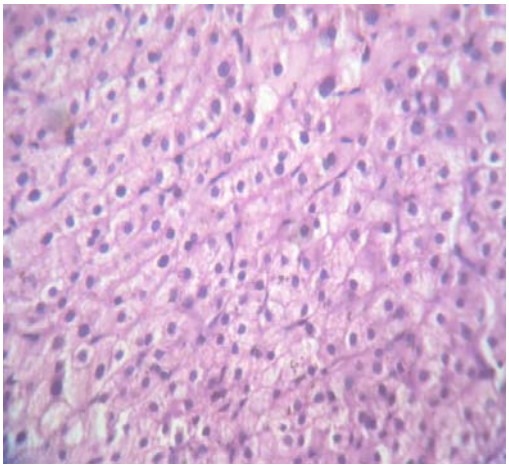
**HISTOLOGICAL GRADE-OBSERVATIONS-DIAGRAM**



## Minimal Macro-Steatosis

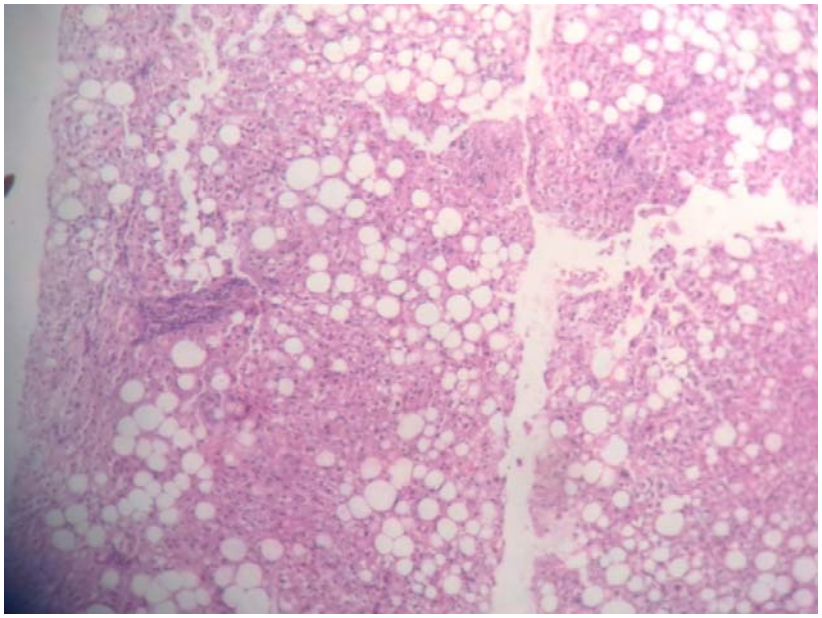


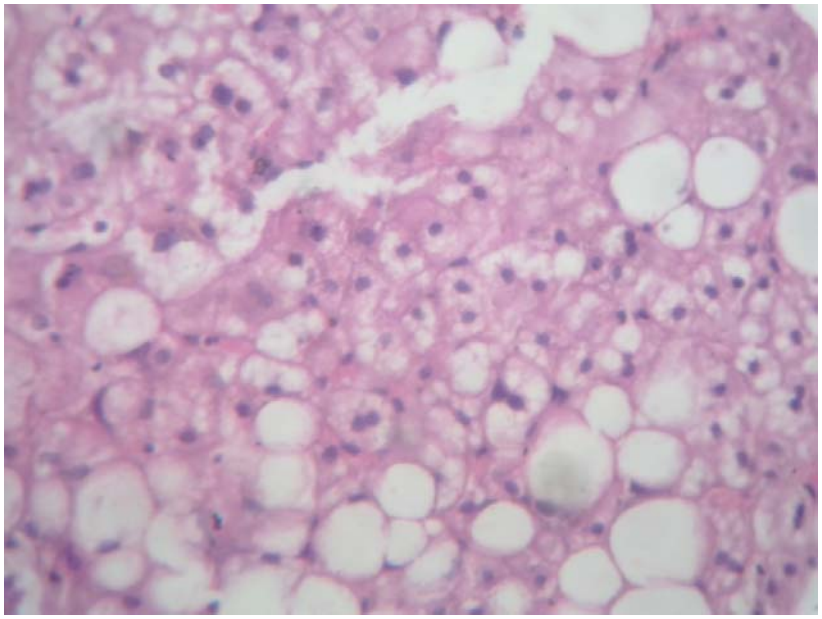




## Grade I

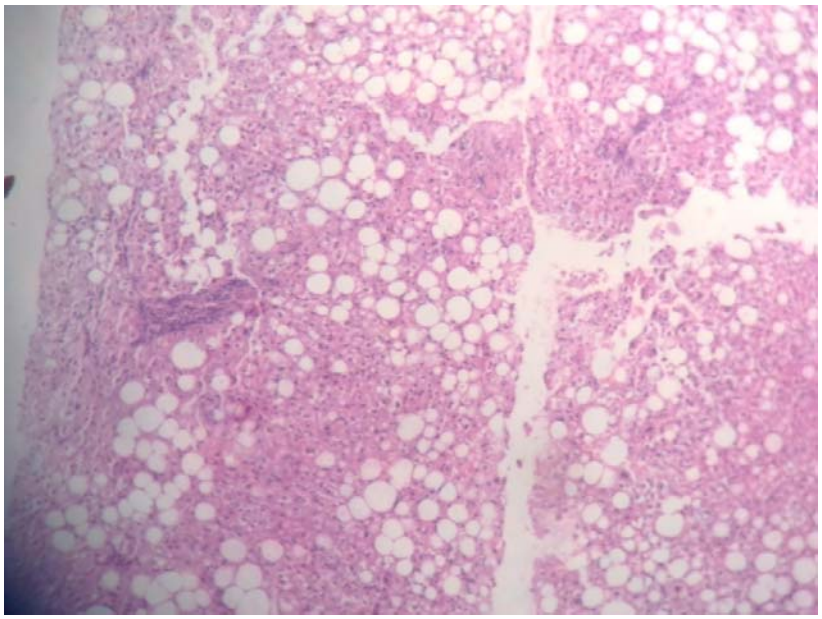
## Macro-Steatosis

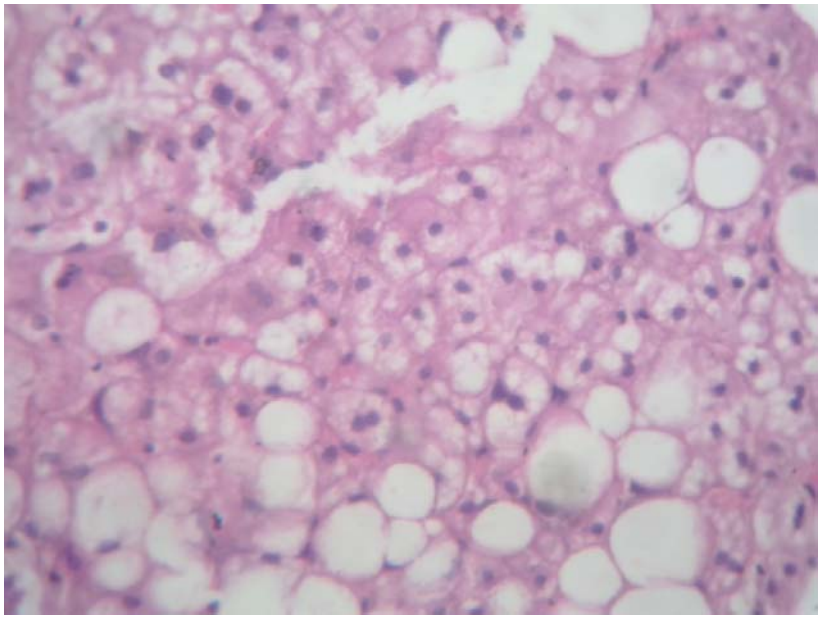




## Grade II

## Macro-Steatosis





**Grade III**

**Macro-Steatosis**

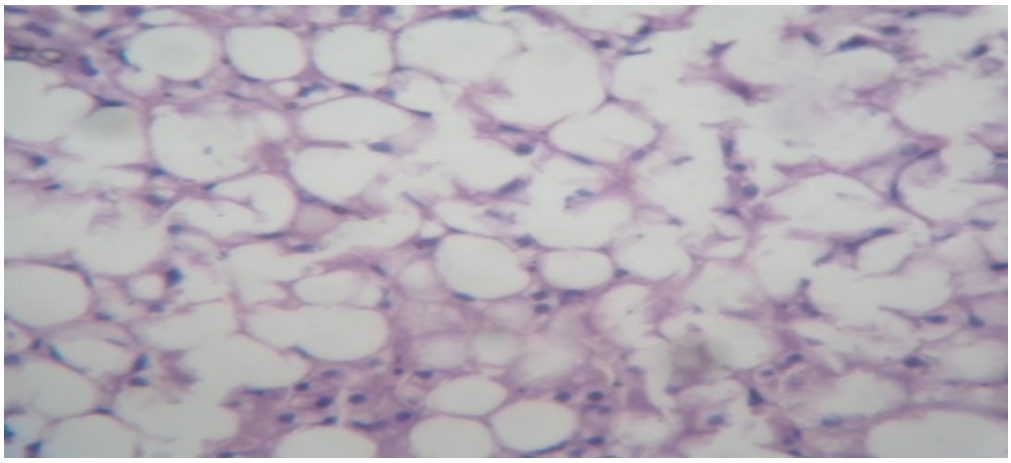


**Table 6**

**One way ANOVA to compare mean values between Histology**

| | Histology | N | Mean | Std. Dev | Min | Max | P-Value |
|---|---|---|---|---|---|---|---|
| CT HU Liver-spleen | Minimal | 5 | 13.00 | 4.36 | 8.00 | 18.00 | 0.001 |
| | Mild | 9 | 15.11 | 4.17 | 6.00 | 19.00 | |
| | Moderate | 12 | 20.25 | 2.05 | 17.00 | 23.00 | |
| | Severe | 4 | 24.25 | 0.96 | 23.00 | 25.00 | |
| | Total | 30 | 18.03 | 4.85 | 6.00 | 25.00 | |

**Table 7**

**Tukey HSD Post Hoc Tests to compare multiple pairwise comparisons**

| Dependent Variable | Pairs | | Mean Difference | P-Value |
|---|---|---|---|---|
| CT HU Liver-spleen | Minimal | Mild | -2.111 | 0.640 |
| | | Moderate | -7.250 | 0.001 |
| | | Severe | -11.250 | 0.001 |
| | Mild | Moderate | -5.139 | 0.006 |
| | | Severe | -9.139 | 0.001 |
| | Moderate | Severe | -4.000 | 0.157 |

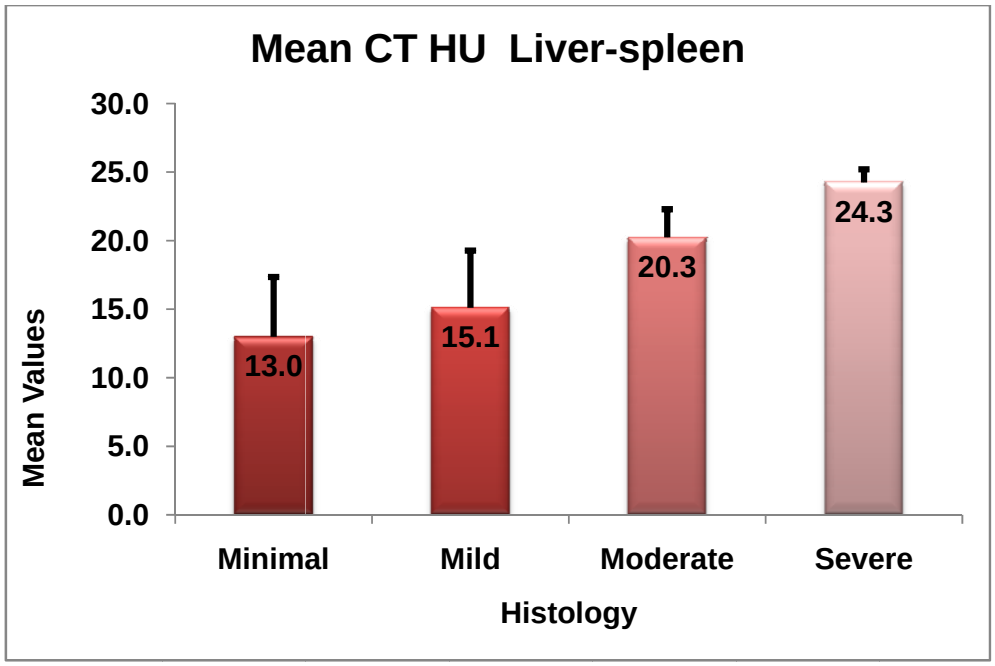
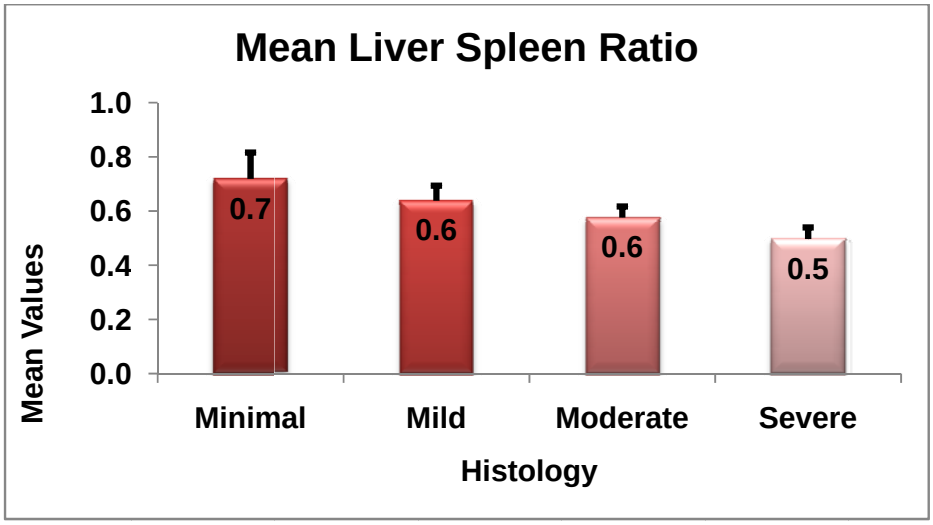

Mean CT HU Liver-spleen
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Mean Values
13.0
15.1
20.3
24.3
Minimal
Mild
Moderate
Severe
Histology

**Table 8**

**One way ANOVA to compare mean values between Histology**

| | Histology | N | Mean | Std. Dev | Min | Max | P-Value |
|---|---|---|---|---|---|---|---|
| Liver Spleen Ratio | Minimal | 5 | 0.719 | 0.097 | 0.620 | 0.830 | 0.001 |
| | Mild | 9 | 0.638 | 0.056 | 0.580 | 0.750 | |
| | Moderate | 12 | 0.576 | 0.041 | 0.530 | 0.670 | |
| | Severe | 4 | 0.497 | 0.043 | 0.460 | 0.540 | |
| | Total | 30 | 0.608 | 0.087 | 0.460 | 0.830 | |



**Tukey HSD Post Hoc Tests to compare multiple pairwise comparisons**

| Dependent Variable | Pairs | | Mean Difference | P-Value |
|---|---|---|---|---|
| Liver Spleen Ratio | Minimal | Mild | 0.081 | 0.081 |
| | | Moderate | 0.143 | 0.001 |
| | | Severe | 0.222 | 0.001 |
| | Mild | Moderate | 0.062 | 0.092 |
| | | Severe | 0.141 | 0.002 |
| | Moderate | Severe | 0.079 | 0.110 |

**Tukey HSD Post Hoc Tests to compare multiple pairwise comparisons**

| Dependent Variable | Pairs | | Mean Difference | P-Value |
|---|---|---|---|---|
| CT HU Liver | Minimal | Mild | 4.111 | 0.233 |
| | | Moderate | 5.167 | 0.072 |
| | | Severe | 6.250 | 0.090 |
| | Mild | Moderate | 1.056 | 0.920 |
| | | Severe | 2.139 | 0.783 |
| | Moderate | Severe | 1.083 | 0.959 |

**Tukey HSD Post Hoc Tests to compare multiple pairwise comparisons**

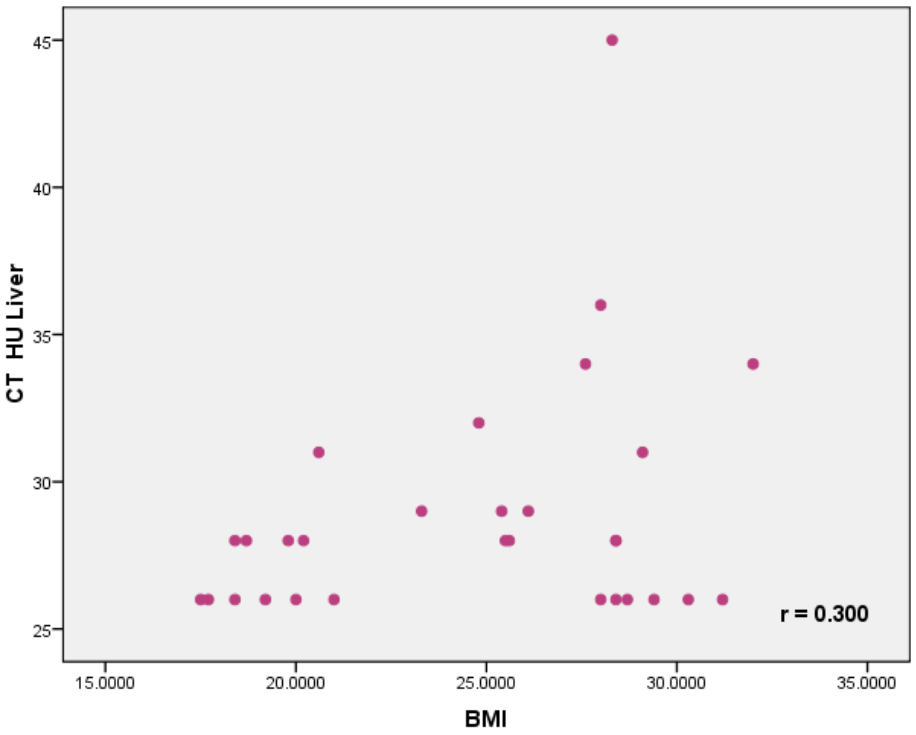
| Dependent Variable | Pairs | | Mean Difference | P-Value |
|---|---|---|---|---|
| BMI | Minimal | Mild | -0.249 | 1.000 |
| | | Moderate | 1.173 | 0.967 |
| | | Severe | -1.660 | 0.954 |
| | Mild | Moderate | 1.422 | 0.905 |
| | | Severe | -1.411 | 0.960 |
| | Moderate | Severe | -2.833 | 0.734 |

**Tukey HSD Post Hoc Tests to compare multiple pairwise comparisons**

| Variable | Pairs | | Mean Difference | P-Value |
|---|---|---|---|---|
| Liver Spleen Ratio | Mild | Moderate | .05064 | 0.280 |
| | | Severe | .06243 | 0.608 |
| | Moderate | Severe | .01180 | 0.982 |

# CHARTS

## Correlation Graph



# DISCUSSION

# DISCUSSION

The degree of steatosis in NAFLD patients is usually assessed with invasive technique like liver biopsy [leon A.Adams,et al][7], Because of the invasive method of the liver biopsy and its painful nature of the procedure with moderate complication rate there has always been a need to find alternative less invasive, less painful, quick method to accurately diagnose NAFLD is the need of the hour.

CT scan and MRI scan are well established imaging modalities for diagnosis of various disorders. These imaging modalities can also assess the degree of fat as accurately as histology of liver tissue. This accuracy of grading of fatty liver by CT and MRI has been utilized by various investigators. Olmsted etal large study 420pts with definte NAFLD on imaging and liver biopsy. But only few studies are available [Nathan et al; sheela ramesh; arun j.sanyal et al][1,2,3].

These authors tried to validate CT scan as non invasive diagnostic modality for this purpose, by comparing against gold standard liver biopsy. but their studies have been done in smallnumber [ie., 15 subjects].

Most of the studies are with magnetic resonance image [MRI].few studies are with computerized tomography [Nathan et al][1]. These studies are also small in number.

In our study non contrast computerized tomography scan [nc CT] has been done in all the patients [no of sample size is 30] compared to previous studies the number is doubled.

Initial evaluation of NAFLD requires ultra sound scan of abdomen.just as In previous studies the investigators used USG for initial evaluation. But this USG abdomen scan can be used for screening purpose only. It is not useful for semi quantitative assessment of steatosis.

Non contrast CT scan [nc CT] has been done in both the studies. Because non contrast CT scan will give accurate measurement of fat content of the liver measured as a hounce field unit is compared with nearby organ spleen. Both the studies [our study and the previous study] followed the same method. Use of contrast is avoided because contrast will decrease the liver attenuation in hounce field unit. It will give false positive results.

The diagnostic sensitivity of the CT depends upon the severity of steatosis. HU will fall when more steatosis is present in the liver. In the milder form of steatosis the HU will be in higher values or equal to spleen value.

The study has confirmed the nc CT is useful technique delineating macrosteatosis (HMS) in very high BMI P&S , CT with more HU unit

difference between CTHU liver to spleen is significantly and directly correlated to the histology in HMS.

CT assessment of hepatic steatosis in previous studies was criticized on the basis of limited accuracy to estimate hepatic fat content accurately [etal] but such critisizism cannot be leveled with our datas

Most of the studies conducted earlier [Nathan j.shore etal][1] is not a direct comparison between macrosteatosis to liver HU unit difference, only one study compared [Nathan et al] [1] hepatic macrosteatosis HMS to CT HU – liver difference, those studies are in small number.

The strength of this study,that it is a direct comparison of liver CT attenuation with histological grade of steatosis, it is not included the stage of fibrosis. In our study we have adopted grading of steatosis in four stages namely grade 0 is minimal <5 % of macrosteatosis, grade I is 5-33 % of macrosteatosis, grade II is 33-66 % of macrosteatosis, and grade III is more than 66 % When compared to previous studies [Nathan j.shore etal][1] adapted hepatic macrsteatosis as more than 30 % [HMS].and this value has been compared to hepatic attenuation index in HU and also there is no control arm in the previous mentioned studies [Nathan j.shore etal][1]. To delineate in which grade of HMS will directly correlate to hepatic CT attenuation index.

Nathan j.shore etal[1] in their study have taken biopsy from both lobes of liver. And the biopsy is a wedge biopsy taken at the time of bariatric surgery. The tissue sample size is compared to our study is larger. And also they studied the liver tissue triglyceride's concentration by biochemical methods. But in our study biopsy has been taken by true cut needle biopsy using biopsy gun and the tissue sample is small and only taken from the right lobe of the liver alone, in this study no biochemical analysis of liver tissue is made ,the possibility of false negative results [ if the normal liver tissue in the biopsied sample ]could be possible and a false positive results [a focal nodular fatty liver] may be another possibility to give grade III macro steatosis on histology.

Previous study by qayyum etal. In his study he has included higher BMI patients only [BMI > 30] when compared to this study where in we have included all the patients with BMI starting from 17.5 - 32 . In our study the inclusion criteria is based on the ultra sonogram finding of fatty liver. So that lean NASH can be calculated with our study. Out of 30 patients lean NASH is [0 %].

In various studies sample size is small less than 15 patients [Nathan j.shore etal][1]compared to this study the sample size is 30 subjects. But one drawback of our study, there is no control arm, if a control arm is included we can accurately delineate at which liver HU difference which

we can accurately predict the presence of NAFLD. It could served as a quantitative assessment of NAFLD score. The control arm was not designed due to the ethical point of view as well as risk of liver biopsy in normal subjects. Even though if the normal subject found to be detected having NAFLD. There is no definite treatment option available till Date. Also associated risk of radiation exposure in normal subjects for an investigation for a non clinical purpose. The studied patients under went plain CT abdomen, there is a life time risk of medical radiation but is a modest radiation exposure and also the abdominal region only exposed to radiation and not to the entire body.

# CONCLUSION

# CONCLUSION

1] There is definite correlation between non contrast computerized tomography [nc CT] with liver biopsy in this study [p value 0.001]

2] Hence non contrast computerized tomography [nc CT] can be used as a sole investigation for defining NAFLD. invasive liver biopsy can be used for borderline or indeterminate cases

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# ANNEXURES

# CONSENT FORM

**DESCRIPTION:** You are invited to participate in a research study on liver disease. We are going to assess the normal values of liver biochemistry ,liver scan and liver tissue biopsy in healthy adults.

**PROCEDURES:** You will be asked to do ultra sound scan , CT-Scan, Liver biopsy (small piece of liver tissue by a small needle biopsy )and Blood test provide a sample of blood (1 tablespoon). The blood will be taken from your arm at the same time you are going to donate the blood.

The results of the study of your samples will be used for research purposes only and you will not be told the results of the tests.

**RISKS AND BENEFITS:** there are mild risks of bleeding from liver puncture site associated pain with this study.

**TIME INVOLVEMENT:** Post liver biopsy you have to stay for one day for observation of any complication

**PAYMENTS:** You will not be paid to participate in this study.

I, _____ , hereby consent to do USG abdomen, CT abdomen , liver biopsy ,Blood sample which I have donated as a voluntarily for the purpose of estimating the function of the liver in normal individuals. I have understood that this sample will be used for research and the results will not be available to me. I have also understood that this does not involve any additional procedure**.**

**Witness – Signature, Name and address**

**Signature of the donor**

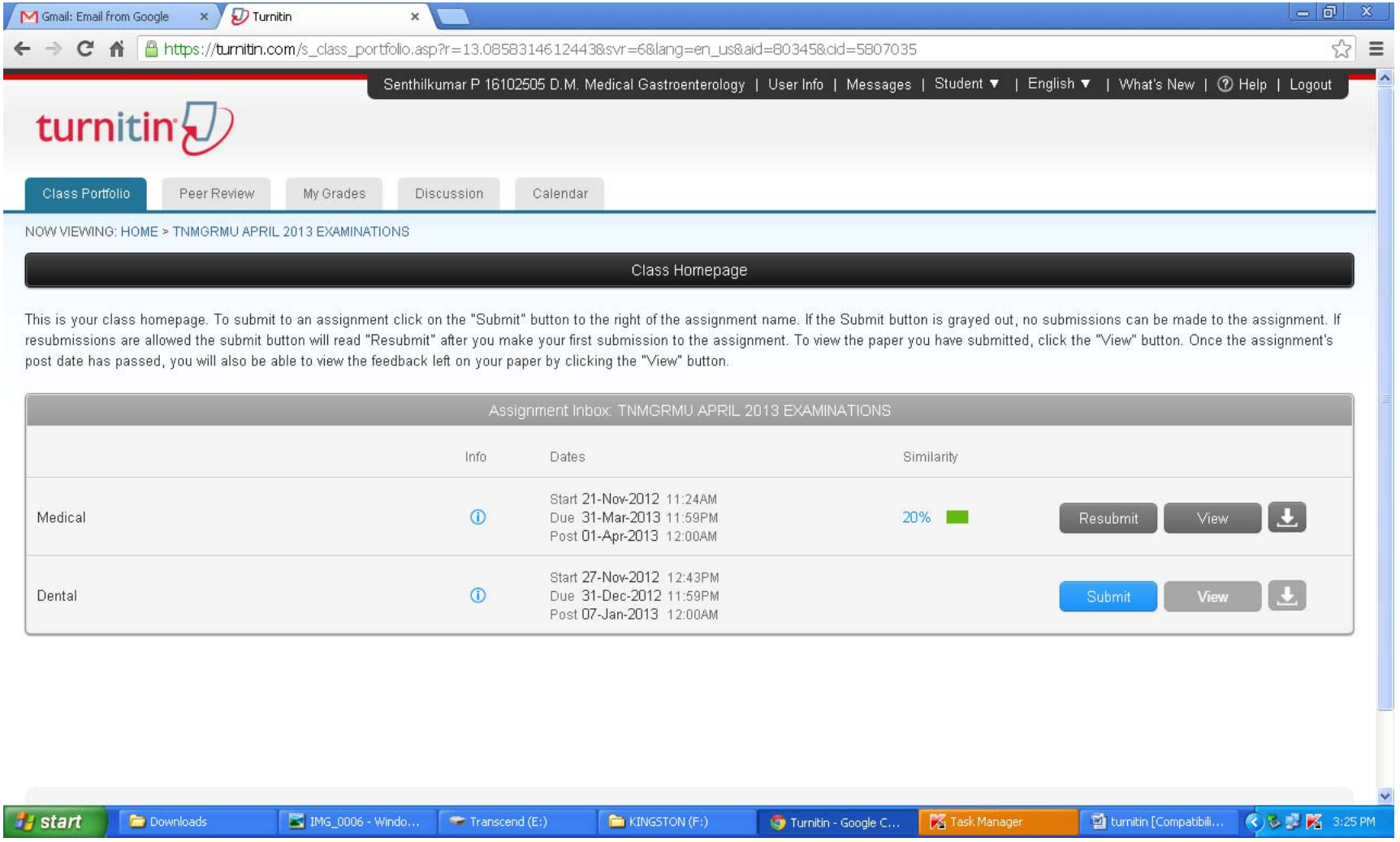
**Name of the Donor**

# PROFORMA

| | |
|---|---|
| NAME | |
| AGE/SEX | |
| GE.No. | |
| CBC | |
| LFT | |
| PT/INR | |
| BT/CT | |
| HBsAg | |
| AntiHCV | |
| BLOOD SUGAR<br>F/PP | |
| BMI<br>WAIST/HIP | |
| ALOHOL CONSUPTION<br>QUANTITY IN GRAMS | |
| USG ABDOMEN | |
| CT ABDOMEN<br>LIVER/SPLEEN RATIO<br>LIVER-SPLEEN INDEX | |
| LIEVER BIOPSY<br>LENGTH<br>FINDING<br>COPLICATION | |

## MASTER CHART

| SL.No | NAME | AGE | SEX | HEIGHT | WEIGHT | BMI | USG abdomen | CT HU Liver | CT HU spleen | CT HU Liver-spleen | HISTOLOGY | LFT1 | LFT-AST | LFT-ALT | LFT-SAP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | raja | 29 | m | 155 | 75 | 31.2 | 3 | 26 | 49 | -23 | 3 | 1.12 | 25.7 | 39.9 | 131 |
| 2 | banumathi | 32 | f | 155 | 70 | 29.1 | 1 | 31 | 52 | -21 | 2 | 1.4 | 29 | 32 | 120 |
| 3 | devaki | 60 | f | 152 | 68 | 29.4 | 2 | 26 | 45 | -19 | 2 | 0.9 | 34 | 42 | 92 |
| 4 | rangasamy | 55 | m | 168 | 72 | 25.5 | 1 | 28 | 47 | -19 | 1 | 0.9 | 30 | 23 | 83 |
| 5 | yoganand | 57 | m | 168 | 80 | 28.3 | 2 | 45 | 54 | -9 | 0 | 1.1 | 23 | 29 | 92 |
| 6 | aisha bee | 47 | f | 150 | 72 | 32 | 1 | 34 | 42 | -8 | 0 | 0.7 | 59 | 44 | 152 |
| 7 | purushothaman | 39 | m | 169 | 80 | 28 | 1 | 36 | 48 | -12 | 1 | 0.9 | 36 | 39 | 75 |
| 8 | ladly | 32 | m | 152 | 70 | 30.3 | 2 | 26 | 48 | -22 | 2 | 1.1 | 94 | 86 | 132 |
| 9 | ram mohan | 53 | m | 155 | 69 | 28.7 | 1 | 26 | 49 | -23 | 2 | 1.3 | 21 | 26 | 102 |
| 10 | prabha | 44 | f | 153 | 45 | 19.2 | 2 | 26 | 48 | -22 | 2 | 1 | 56 | 76 | 134 |
| 11 | ramasamy | 55 | m | 165 | 50 | 18.4 | 3 | 26 | 42 | -6 | 1 | 0.7 | 34 | 36 | 120 |
| 12 | ayisha bevi | 47 | f | 156 | 69 | 28.4 | 1 | 28 | 45 | -17 | 1 | 1.2 | 29 | 23 | 84 |
| 13 | prasanth | 44 | m | 160 | 65 | 25.4 | 2 | 29 | 54 | -25 | 3 | 0.9 | 102 | 109 | 196 |
| 14 | jananki | 39 | f | 158 | 50 | 20 | 1 | 26 | 42 | -18 | 0 | 0.7 | 34 | 31 | 98 |
| 15 | gopi | 43 | m | 162 | 52 | 19.8 | 1 | 28 | 48 | -20 | 2 | 0.8 | 34 | 36 | 102 |
| 16 | nisha | 47 | f | 158 | 71 | 28.4 | 2 | 26 | 57 | -25 | 3 | 4.1 | 32 | 34 | 98 |
| 17 | priya | 34 | f | 157 | 68 | 27.6 | 2 | 34 | 51 | -17 | 2 | 0.7 | 231 | 246 | 163 |
| 18 | jothi | 42 | f | 154 | 48 | 20.2 | 2 | 28 | 45 | -17 | 2 | 0.8 | 24 | 19 | 98 |
| 19 | amudha | 48 | f | 160 | 48 | 18.7 | 2 | 28 | 45 | -16 | 1 | 2.1 | 19 | 17 | 102 |
| 20 | lalitha | 51 | f | 149 | 63 | 28.4 | 1 | 28 | 45 | -17 | 1 | 0.8 | 83 | 96 | 159 |
| 21 | kumar | 45 | m | 162 | 54 | 20.6 | 2 | 31 | 45 | -14 | 0 | 1.8 | 19 | 17 | 109 |
| 22 | muniammal | 48 | m | 158 | 70 | 28 | 1 | 26 | 45 | -19 | 1 | 0.8 | 64 | 96 | 128 |
| 23 | yogas | 57 | m | 168 | 70 | 24.8 | 1 | 32 | 45 | -13 | 1 | 0.9 | 124 | 34 | 102 |
| 24 | vetriselvan | 35 | m | 159 | 53 | 21 | 2 | 26 | 56 | -24 | 3 | 1.8 | 34 | 31 | 103 |
| 25 | vijayalakshmi | 39 | f | 155 | 56 | 23.3 | 1 | 29 | 45 | -16 | 0 | 0.7 | 96 | 96 | 104 |
| 26 | sangeetha | 40 | f | 154 | 62 | 26.1 | 2 | 29 | 48 | -19 | 2 | 2.1 | 19 | 20 | 96 |
| 27 | noorjagan | 42 | f | 150 | 42 | 17.5 | 2 | 26 | 48 | -19 | 2 | 0.9 | 47 | 51 | 102 |
| 28 | anandvalli | 45 | f | 143 | 68 | 25.6 | 1 | 28 | 45 | -17 | 1 | 1.2 | 29 | 34 | 106 |
| 29 | thiru | 51 | m | 167 | 47 | 17.7 | 2 | 26 | 48 | -22 | 2 | 1 | 34 | 39 | 123 |
| 30 | parthiban | 54 | m | 165 | 50 | 18.4 | 2 | 28 | 50 | -22 | 2 | 1 | 29 | 34 | 96 |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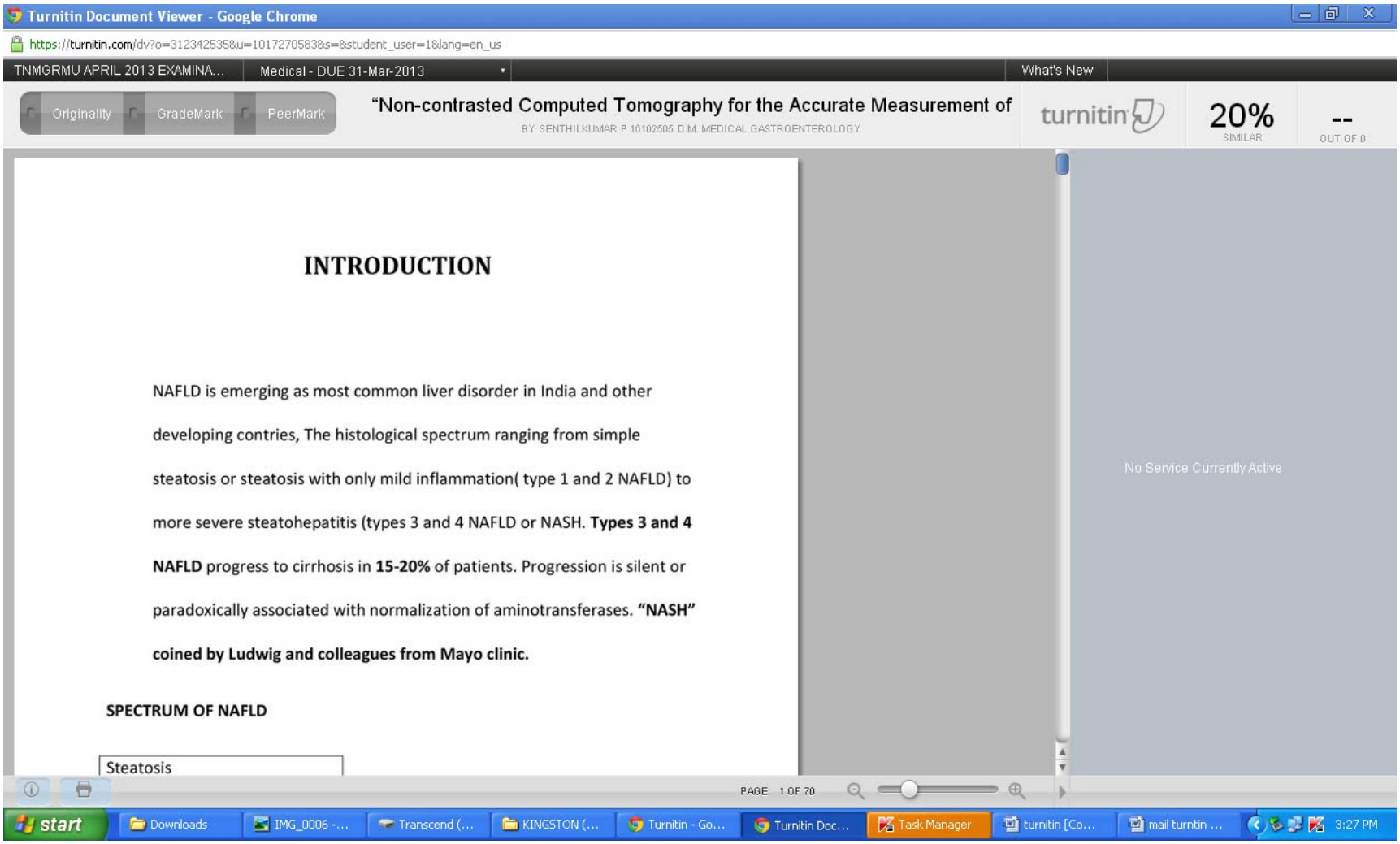
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INTRODUCTION
NAFLD is emerging as most common liver disorder in India and other developing contries, The histological spectrum ranging from simple steatosis or steatosis with only mild inflammation( type 1 and 2 NAFLD) to more severe steatohepatitis (types 3 and 4 NAFLD or NASH. Types 3 and 4 NAFLD progress to cirrhosis in 15-20% of patients. Progression is silent or paradoxically associated with normalization of aminotransferases. "NASH" coined by Ludwig and colleagues from Mayo clinic.
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Steatosis
No Service Currently Active
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